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BACLOFEN FOR REDUCTION OF CRAVING AND ANXIETY DEPRESSION IN ALCOHOL DEPENDENCE SYNDROME: A PRELIMINARY INVESTIGATION

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ABSTRACT

Introduction: Alcohol dependence affects nearly 10% of the population, both in the USA and in Europe, and poses serious threat to public health by increasing morbidity & mortality. Treatment for alcohol dependence consists of psychological, social and pharmaceutical interventions. The ability of baclofen to reduce alcohol craving and promote alcohol abstinence in alcohol-dependent individuals has been observed in some open-label studies.

Materials and method: Thirteen patients (12 male & 1 female) who were self referred were taken from de-addiction clinic of I.M.S, B.H.U. All patients were assessed for eligibility and were consequently admitted. Thirteen patients (12 male & 1 female) were taken from de-addiction clinic of I.M.S, B.H.U. All patients were admitted. The following tools were administered: Hamilton's anxiety; Hamilton's depression scale; Penn craving scale; Emergent Side effects Semi-structured interview; Abstinence Semi-structured interview. All patients were assessed on baseline using semi-structured proforma and relevant history. It was 12 week long follow up study. Patients were assessed on baseline and at 2, 4, 6, 8, 10 and 12 weeks.

Results: Out of 13 patients enrolled, 2 patients dropped at 1st follow up, only 11 patients completed the (10 male ,1 female) study. Out of 11 patients, 9 patients (8 males and 1 female) reported complete abstinence and 2 male patients had significant reduction in craving, but continued minimal intake of alcohol. Also there was a declining trend in cumulative abstinence as measured by number of standard drinks/day. Treatment adherence was 85%.

Discussion: Total abstinence was present in 8 patients. In the present study the beneficial effect of baclofen in maintaining abstinence has been attributed to its capacity to reduce anxiety, this study also hypothesized that baclofen may also have an antidepressant effect on alcohol-abstinent participants. Also the GABA action of baclofen is beneficial.

Conclusion: Drug was found to be cost effective as well safe for use on an out-patient basis.

INTRODUCTION:

Alcohol dependence affects nearly 10% of the population, both in the USA and in Europe, and poses serious threat to public health by increasing morbidity & mortality[1]. Per capita alcohol consumption is highest in France, followed by Germany, Australia, and the United Kingdom. All are above the per capita consumption levels in the U.S.[2]. India is usually considered to be dry country mostly due to cultural affiliations[3]. According to a household survey, the prevalence of alcohol use was 21%[4]. The prevalence of current use of alcohol ranged from a low of 7% in the western state of Gujarat (officially under Prohibition) to 75% in the North-eastern state of Arunachal Pradesh. There is also an extreme gender difference as prevalence among women is less than 5% but is much higher in the North-eastern states[5,6].

GLOBAL BURDEN:

In 2012, 3.3 million deaths, or 5.9 percent of all global deaths (7.6 percent for men and 4.0 percent for women), were due to alcohol consumption [7].In 2014, according to World Health Organization alcohol contributed to more than 200 diseases and injury-related health conditions, most notably liver cirrhosis, cancers, and injuries[8].In 2012, 5.1 percent of the burden of disease and injury worldwide (139 million disability-adjusted life-years) was attributable to alcohol consumption[7]. Treatment for alcohol dependence consist of psychological, social and pharmaceutical interventions [9,10]. Only a few medications are approved for this purpose by FDA.

Baclofen is a γ-aminobutyric acid (GABA) B-receptor agonist and its mechanism has been proposed to be GABA mediated inhibition of dopamine neurons thereby inhibiting dopamine mediated reinforcing behaviour and at present is approved to treat muscular spasticity. Human studies with alcohol-dependent patients have shown the safety and the efficacy of baclofen as a pharmacotherapy agent for treatment of dependence. The ability of baclofen (10 mg thrice a day) to reduce alcohol craving and promote alcohol abstinence in alcohol-dependent individuals has already been observed in some open-label studies[11,12].Most of the studies have reported baclofen at the dose of 10 mg in three divided doses. However, anecdotal reports have hypothesized the ability of high doses of baclofen (up to 140 and 270 mg/day) to reduce alcohol craving and consumption [13,14]. Baclofen at the dose of 60 to 80 mg has already been tested in other addictions, i.e. cocaine dependence[15,16].

Despite being freely available there are very few Indian studies regarding use of baclofen in alcohol dependence syndrome. The present study is a preliminary investigation to assess its safety and efficacy.

AIM OF STUDY:

To assess the safety and effectiveness of Baclofen in reducing symptoms of craving and anxiety in alcohol dependence

PATIENTS AND METHODS:

Thirteen patients (12 male & 1 female) who were self referred were taken from de-addiction clinic of I.M.S, B.H.U which is a tertiary care centre. All patients were assessed for eligibility and were consequently admitted.

Inclusion criteria:

- Age above 18 years to 60 years.
- Meeting ICD-10 criteria for alcohol dependence.
- Alcohol intake – at least 2 heavy drinking days / week or > 21 drinks / week in men and > 4 drinks/week for female, for 4 weeks prior to study intake[17]
- Accompanied by a family member.

Exclusion criteria:

- Severe medical co-morbidity.
- Co-morbid psychiatric abnormality.
- Coming alone or non available family member.
- Concomitant use/ abuse/dependence of other substances.

TOOLS:

- Anxiety – Hamilton's anxiety [18]
- Depression - Hamilton's depression scale.[19]
- Craving – Penn craving scale[20]
- Emergent Side effects Semi-structured interview
- Abstinence – Semi-structured interview

METHOD:

All included patients were assessed on baseline using semi-structured proforma and relevant history was taken. Routine haematological investigations were

done in each patient. If patient was having active withdrawal then subjects were treated for withdrawal and thereafter enrolled into the study.

It was 12 week long follow up study. All participants provided written, informed consent before enrolment. Study was approved by the institute ethical committee. All patients were given 10mg Baclofen twice a day for 1 week and then 10mg thrice a day for 10 week. Patients were assessed on baseline and at 2, 4, 6, 8, 10 and 12 weeks. At each follow up patients were assessed on Hamilton Anxiety rating scale, Hamilton Depression rating scale, Penn craving scale, side effects and relevant semi structured interview to check for abstinence.

RESULTS:

Out of 13 patients enrolled, 2 patients dropped at 1st follow up, only 11 patients completed the (10 male ,1 female) study. Out of 11 patients, 9 patients (8 males and 1 female) reported complete abstinence and 2 male patients had significant reduction in craving, but continued minimal intake of alcohol. Patient's mean HAMDRS scores were around 28 at 2 weeks follow up and 5 at 12 weeks (Fig 1). Similarly there was a declining trend in HAMARS (27 at 2 weeks and 6 at the end of 12 weeks) Fig 2,Penn craving score (54 at 2 weeks and 18 at 12 weeks) Fig 3.

Also there was a declining trend in cumulative abstinence as measured by number of standard drinks/day. Average total drinks/day of all patients at follow up at 2 weeks were 20/day, similarly there was a declining trend; drinks per day decreased to 16 at 4 weeks follow up and they were 12, 7, 4 and 1 at 6, 8, 10 and 12 weeks respectively. (Fig4)

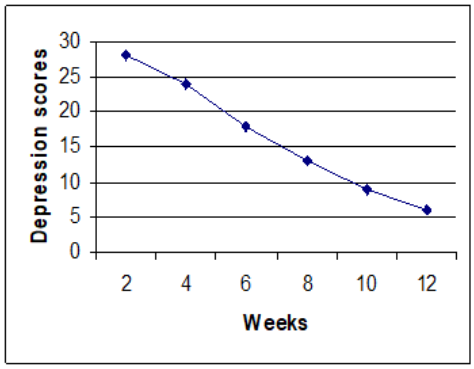

Fig. 1: HAMD scores

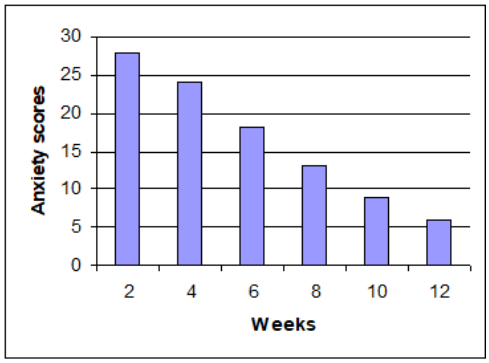

Fig. 2: HAMA scores

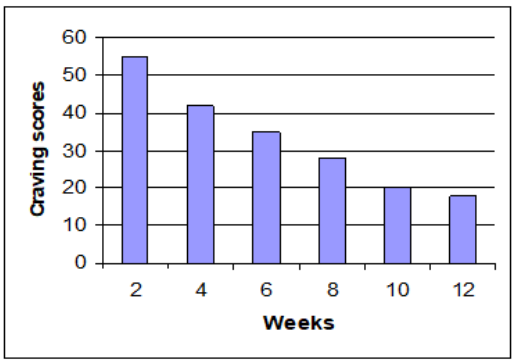

Fig. 3: Penn Craving score

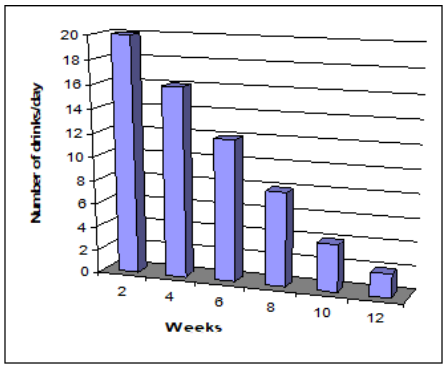

Fig. 4: Cumulative abstinence score

OUTCOME:

Treatment adherence was 85%. Side effects noted during follow up were headache, tiredness, vertigo and somnolence, which are the commonest side effects reported. Total abstinence was present in 8 patients according to history given by family members. Drug was found to be cost effective as well safe for use on an out-patient basis.

DISCUSSION:

Baclofen is a GABA b agonist and has significant anxiolytic properties and clinical data suggest that it is effective in PTSD[21]panic disorder[22] and alcohol-dependence syndrome(23) Depressive and anxiety symptoms are important to address in subjects with alcohol dependence, as they are a known risk factor for relapse in abstinent individuals[24]. In a recent study [25] the beneficial effect of baclofen in maintaining abstinence has been attributed to its capacity to reduce anxiety, this study also hypothesized that baclofen may also have an antidepressant effect on alcohol-abstinent participants. In our trial, similar findings came, as evidenced by sequential lowering of HAMARS & HAMDRS scores. Although to begin with, this could be subjected to bias as sample population was not matched and statistical significance could not be established due to small sample size. Also trial was not blinded which could also cause clinician bias. Although one Indian study could not find statistically significant reduction in HAMD rating scores [26].This open label trial provided same findings. The study had several methodological limitations as sample size was small to begin with; no other agent was used to compare effects of baclofen. Also trial was not blinded and it could have contributed to biasing in scoring by clinician. But safety of the agent could be easily established from this open label trial as no significant side effects occurred in 12 weeks follow up.

Adherence rate in our trial was 85% and there was significant reduction in craving as well, this finding was in accordance with an Italian study by Addolorato in 2002, it was either due to low side effects and good tolerability of baclofen or could be due to lowering of craving, anxiety and depression but Garbutt et al. did not find baclofen to be any more effective than placebo in the primary outcome measure, that is, percentage of heavy drinking days, or in the secondary outcome measures of percentage of abstinent days, craving, or anxiety measures. This discrepancy could also be explained by the method of recruitment in the study. The Addolorato trials recruited participants who were seeking treatment, as in our trial, patients were self referred, whereas the Garbutt trial recruited through advertising. This may have resulted in more dependent and highly motivated participants recruited in the Italian trials although our participants were not matched for confounding factors, therefore this adherence rate could be affected by biasing[27,28]. According to one Indian study by Gupta et al, most of the relapses are in first 4 weeks of the treatment and as duration progressed, the rates of lapse or relapse declined in baclofen-treated participants. Therefore, it recommended that baclofen should be continued for 12 weeks; similar pattern of treatment was followed in our trial [26].

FUTURE DIRECTIONS:

As our trial was confounded by many factors, we propose a cross over double blinded controlled drug trial comprising of larger sample size and multicentre trials.

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